L1 ANSWER 1 OF 3 WPIDS (C) 2002 THOMSON DERWENT
AN 1992-127300 [16] WPIDS
DNC C1992-059283
TI New peptide for angiotensin conversion inhibitor - also inhibits bradykinin inactivation, useful for prevention, treatment and diagnosis of hypertension.
DC B04 D16
PA (NISY) NIPPON SYNTHETIC CHEM IND CO
CYC 1
PI JP 04069398 A 19920304 (199216)* 6p <--
JP 3012291 B2 20000221 (200014) 6p C07K007-06
ADT JP 04069398 A JP 1990-179842 19900706; JP 3012291 B2 JP 1990-179842 19900706
FDT JP 3012291 B2 Previous Publ. JP 04069398
PRAI JP 1990-179842 19900706
IC A61K037-64; C07K007-06; C07K099-00; C12N009-99; C12P021-06
ICM C07K007-06
ICS A61K037-64; A61K038-55; C07K099-00; C12N009-99; C12P021-06
ICA A61K031-00
AB JP 04069398 A UPAB: 19931006
New peptide has a frame of Pro-Arg-His-Gln-Gly (I). Prepn. of the peptide (I) is by hydrolysing protein with thermolysin. An angiotensin converting enzyme inhibitor contains the peptide (I) as an active component.

As protein, actin or fish meat pref. dried bonito is used.

USE/ADVANTAGE - The peptide has an excellent angiotensin conversion inhibiting effect, depression effect, bradykinin inactivation inhibiting effect, it can be used for prophylaxis and treatment of essential hypertension, renal hypertension, adrenal hypertension, etc., and for a diagnostic agent of these diseases.

In an example, to dried bonito (5g), water (50 ml) was added, and homogenised enough, next, boiled at 100 deg.C for 10 min., and standing. Thermolysin (20mg) was added, and hydrolysed at 37 deg.C, pH 7, for 3 hrs. After cooling, concn. by centrifugation and purified by HPLC (ODS-, pH- and CN-column). Aminoacid sequence was analysed by automatic Edman decompsn. method. H-Ile-Val-Gly-Arg-Pro-Arg-His-Gln-Gly-OH was obtained. TLC (n-buOH:AcOH:pyridine:H2O = 15:3:10:12, Rf:0.22, m.p. 81.2 Deg.C, (alpha)D24: (C = 1.0, H2O); -86.3. (0/0)
0/0
FS CPI
FA AB; DCN
MC CPI: B04-C01A; B12-F05A; B12-G01; B12-K04A2; D05-H09

L1 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1995:664949 CAPLUS
DN 123:65813
TI Hexapeptides from protease hydrolyzate of sardine muscle and angiotensin converting enzyme inhibitor
IN Suetsuna, Kunio
PA Suetsuna Yoko, Japan
SO Jpn. Kokai Tokkyo Koho, 13 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM C07K007-06
ICS A61K037-64; C12N009-99
CC 63-4 (Pharmaceuticals)
Section cross-reference(s): 7, 34
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 06340692	A2	19941213	JP 1992-159954	19920508 <--
JP 07074236	B4	19950809		

AB Five hexapeptides including H-Leu-Val-His-Pro-Glu-Glu-OH (I), H-Leu-Val-Leu-His-Pro-Lys-OH (II), H-Leu-Val-Lys-His-Pro-Gly-OH (III), H-Leu-Val-Tyr-Pro-Ile-Glu-OH (IV), and H-Leu-Lys-Tyr-Pro-Ile-Glu-OH (V) were isolated were isolated from a protease hydrolyzate of sardine muscle and also prepd. by the solid phase method using an Applied Biosystems peptide synthesizer 430A, a Merrifield resin, and N-Boc-protected amino acids. An angiotensin converting enzyme inhibitor contains one of the above hexapeptides as an active ingredient. I - V in vitro showed IC50 of (1.3-4.2) .times. 10-6 M for inhibiting angiotensin converting enzyme and at 50 mg/kg i.v. in vivo significantly lowered the blood pressure of spontaneously hypertensive rats.
ST hexapeptide protease hydrolyzate sardine muscle; angiotensin converting enzyme inhibitor; antihypertensive hexapeptide
IT Antihypertensives
Sardine
(isolation of hexapeptides from protease hydrolyzate of sardine muscle and angiotensin converting enzyme inhibitors and antihypertensives)
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hexa-, isolation of hexapeptides from protease hydrolyzate of sardine muscle as angiotensin converting enzyme inhibitors and antihypertensives)
IT 9001-75-6, Pepsin
RL: CAT (Catalyst use); USES (Uses)
(catalyst for enzyme hydrolysis of sardine muscle in prepn. of hexapeptides as angiotensin converting enzyme inhibitors and antihypertensives)
IT 164719-24-8P, H-Leu-Val-His-Pro-Glu-Glu-OH 164719-25-9P, H-Leu-Val-Leu-His-Pro-Lys-OH 164719-26-0P, H-Leu-Val-Lys-His-Pro-Gly-OH 164719-27-1P, H-Leu-Val-Tyr-Pro-Ile-Glu-OH 164719-28-2P, H-Leu-Lys-Tyr-Pro-Ile-Glu-OH
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(isolation of hexapeptides from protease hydrolyzate of sardine muscle and synthetic prepn. as angiotensin converting enzyme inhibitors and antihypertensives)

```
     (FILE 'HOME' ENTERED AT 12:52:45 ON 09 NOV 2001)

     INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
     DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 12:52:58 ON
     09 NOV 2001
               SEA ANGIOTENSIN(P)(FISH)
               ---------
               3    FILE ADISALERTS
               0*   FILE ADISNEWS
               2    FILE AGRICOLA
              41    FILE AQUASCI
               2    FILE BIOBUSINESS
               1*   FILE BIOCOMMERCE
             132    FILE BIOSIS
              16*   FILE BIOTECHABS
              16*   FILE BIOTECHDS
              29*   FILE BIOTECHNO
              13    FILE CABA
               2    FILE CANCERLIT
             194    FILE CAPLUS
                SEA ANGIOTENSIN(P)(FISH) AND ILE TYR
                ---------
                0*   FILE ADISNEWS
                0*   FILE BIOCOMMERCE
                0*   FILE BIOTECHABS
                0*   FILE BIOTECHDS
                0*   FILE BIOTECHNO
                0*   FILE CEABA-VTB
                0*   FILE CIN
                1    FILE DDFU
                1    FILE DRUGU
                0*   FILE ESBIOBASE
                0*   FILE FOMAD
                0*   FILE FOREGE
                0*   FILE FROSTI
                0*   FILE FSTA
                0*   FILE KOSMET
                0*   FILE MEDICONF
                0*   FILE NTIS
                0*   FILE PASCAL
L1               QUE ANGIOTENSIN(P)(FISH) AND ILE TYR
                 ---------

     FILE 'DRUGU' ENTERED AT 12:54:33 ON 09 NOV 2001
L2             1 S L1

     FILE 'USPATFULL' ENTERED AT 12:55:09 ON 09 NOV 2001
L3             0 S ANGIOTENSIN(P)(FISH) AND ILE TYR
L4            86 S ANGIOTENSIN AND ILE TYR
L5             7 S ANGIOTENSIN AND ILE TYR AND ILE VAL ARG ASP
L6            38 S ANGIOTENSIN(P)FISH

     FILE 'REGISTRY' ENTERED AT 13:03:37 ON 09 NOV 2001
L7           198 S IVGRPRHQG/SQSP
L8             1 S IVRD/SQEP

     FILE 'CAPLUS' ENTERED AT 13:11:28 ON 09 NOV 2001
L9             1 S L8
L10            4 S IVRD OR ILE VAL ARG ASP
```

```
     INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
     DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 13:13:42 ON
     09 NOV 2001
                SEA ILE VAL ARG ASP
               ---------
                1   FILE IFIPAT
               31   FILE USPATFULL
                3   FILE WPIDS
                3   FILE WPINDEX
L11             QUE ILE VAL ARG ASP
               ---------
                SEA L11 AND (ACE OR ANGIOTENSIN CONVERTING ENZYME)
               ---------
                7   FILE USPATFULL
L12             QUE L11 AND (ACE OR ANGIOTENSIN CONVERTING ENZYME)
               ---------

     FILE 'USPATFULL' ENTERED AT 13:15:29 ON 09 NOV 2001
L13           7 S L12

     FILE 'WPIDS' ENTERED AT 13:17:11 ON 09 NOV 2001
L14           3 S ILE VAL ARG ASP

     FILE 'CAPLUS, WPIDS' ENTERED AT 13:17:53 ON 09 NOV 2001
L15           0 S ILLE LEU TYR
L16          53 S ILE LEU TYR
L17           0 S L16 AND ACE
L18           8 S L16 AND INHIBITOR?
L19           8 DUP REM L18 (0 DUPLICATES REMOVED)
L20           6 S ILE TYR ALA
L21           6 DUP REM L20 (0 DUPLICATES REMOVED)

     FILE 'CAPLUS, EMBASE, MEDLINE, TOXLIT, SCISEARCH' ENTERED AT 13:25:41 ON
     09 NOV 2001
L22          84 S (ILE LEU TYR OR ILE TYR ALA OR ILE LYS TRP OR ILE VAL ARG ASP
L23          55 DUP REM L22 (29 DUPLICATES REMOVED)
L24           8 S L23 AND ANGIOTENSIN
L25          66 S (ILE LEU TYR OR ILE TYR ALA OR ILE VAL ARG ASP)
L26          43 DUP REM L25 (23 DUPLICATES REMOVED)
L27           1 S L26 AND (FISH? OR TUNA? OR BONITO)
L28          90 S ANGIOTENSIN AND (BONITO OR KATSUOBUSI)
L29          61 DUP REM L28 (29 DUPLICATES REMOVED)
L30          90 S ANGIOTENSIN AND (BONITO OR KATSUOBUSI) AND INHIBIT?
L31          61 DUP REM L30 (29 DUPLICATES REMOVED)
L32           3 S L31 AND ILE VAL
L33           0 S L31 AND ILE LEU
L34           1 S L31 AND ILE TYR
```

L24 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 1989:492720 CAPLUS
DN 111:92720
TI Induction of **angiotensin**-converting enzyme inhibitory activity by acid-limited proteolysis of glyceraldehyde 3-phosphate dehydrogenase
AU Kohama, Yasuhiro; Oka, Hiroaki; Yamamoto, Kohji; Teramoto, Tetsuyuki; Okabe, Masaru; Mimura, Tsutomu; Nagase, Yasukazu; Chiba, Yoshiyuki; Fujita, Takao
CS Fac. Pharm. Sci., Osaka Univ., Osaka, 565, Japan
SO Biochem. Biophys. Res. Commun. (1989), 161(2), 456-60
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
TI Induction of **angiotensin**-converting enzyme inhibitory activity by acid-limited proteolysis of glyceraldehyde 3-phosphate dehydrogenase
AB **Angiotensin**-converting enzyme (ACE) inhibitors were obtained from glyceraldehyde 3-phosphate dehydrogenase (GAPDH) prepns. of tuna and porcine muscles by heating at 120.degree. for 5 min in 1M AcOH-20 mM HCl. The inhibitors were then purified by successive chromatogs. The final product from tuna was identified as Pro-Thr-His-**Ile**-**Lys**-**Trp**-Gly-Asp. The porcine ACE inhibitor was found to be Pro-Ala-Asn-**Ile**-**Lys**-**Trp**-Gly-Asp, which was identical to the porcine muscle GAPDH peptide 79-86. These results strongly suggested that the ACE inhibitory octapeptides derived from GAPDH proteins by acid-limited proteolysis at Asp-Pro and Asp-Ala peptide bonds.
ST **angiotensin** converting enzyme glyceraldehyde phosphate dehydrogenase
IT 9001-50-7, Glyceraldehyde phosphate dehydrogenase
RL: BIOL (Biological study)
(**angiotensin**-converting enzyme inhibitors formation by acid-limited proteolysis of)
IT 9015-82-1, **Angiotensin**-converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, formation of, by acid-limited proteolysis of glyceraldehyde phosphate dehydrogenase)
IT 117620-76-5P 122268-34-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of and **angiotensin**-converting enzyme inhibition by, glyceraldehyde phosphate dehydrogenase proteolysis in relation to)

L24 ANSWER 7 OF 8 TOXLIT
AN 1993:21921 TOXLIT
DN CA-118-052448B
TI Peptide, its manufacture, and its use as **angiotensin**-converting enzyme inhibitor.
AU Hasegawa M; Yokoyama K; Yoshikawa M
SO (1992). Jpn. Kokai Tokkyo Koho PATENT NO. 92264095 09/18/92 (Nippon Synthetic Chemical Industry Co., Ltd.).
CY Japan
DT Patent
FS CA
LA Japanese
OS CA 118:52448
EM 199304
TI Peptide, its manufacture, and its use as **angiotensin**-converting enzyme inhibitor.
AB **Angiotensin**-converting enzyme inhibitors, useful as antihypertensives, contain **Ile-Lys-Trp** (I) manufd. by hydrolysis of protein with thermolysin. Homogenized chicken meat was treated with thermolysin at 37.degree. for 5 h to manuf. I, which inhibited **angiotensin**-converting enzyme with IC50 of 1.4 .mu.M. I was also prepd. by peptide coupling by a solid phase method.

IT 9015-82-1, Angiotensin converting enzyme
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(isolation of hexapeptides from protease hydrolyzate of sardine muscle and synthetic prepn. as angiotensin converting enzyme inhibitors and antihypertensives)

=> d all 2

L1 ANSWER 2 OF 2 WPIDS (C) 2002 THOMSON DERWENT
AN 1995-063841 [09] WPIDS
DNC C1995-028365
TI Hexa peptide(s) with angiotensin converting enzyme inhibitory activity - derived from sardine muscle and useful for treating primary hyper tension.
DC B04 D16
PA (SUET-I) SUETSUNA Y
CYC 1
PI JP 06340692 A 19941213 (199509)* 13p C07K007-06 <--
JP 07074236 B2 19950809 (199536) 12p C07K014-46
ADT JP 06340692 A JP 1992-159954 19920508; JP 07074236 B2 JP 1992-159954 19920508
FDT JP 07074236 B2 Based on JP 06340692
PRAI JP 1992-159954 19920508
IC ICM C07K007-06; C07K014-46
ICS A61K037-64; A61K038-55; C12N009-99
ICI C07K123:00
AB JP 06340692 A UPAB: 19950306
Hexapeptides having L-amino acid sequences (1) to (5) are new: (1) Leu-Val-His-Pro-Glu-Glu, (2) Leu-Val-Leu-His-Pro-Lys, (3) Leu-Val-Lys-His-Pro-Gly, (4) Leu-Val-Tyr-Pro-Ile-Glu, or (5) Leu-Lys-Tyr-Pro-Ile-Glu. Also claimed are angiotensin converting enzyme (ACE) inhibiting agent comprising one of the hexapeptides.

USE - The hexapeptides are derived from a hydrolysed soln. of sardine muscle, and is useful for the treatment of primary hypertension, compared to known substances such as L-proline deriv. of bradykinin-activating factor, peptides from collagenase decomposition of gelatin and a peptide from trypsin decomposition of casein most of which showed an antihypertensive effect only when intravenously administered. The hexapeptides are also safe, because they do not cause anaphylactic shock. LD50 is more than 5000mg/kg(oral or rat).

In an example, Sardine muscle was treated to prepare homogenate, incubated with pepsin, subjected to chromatography (2N-NH4OH) to collect peptide fractions 59-69, concentrated, and further subjected to chromatography and HPLC (mobile phase: 0.05% TFA to 25% acetonitrile 10.05% TFA gradient, ratio: 1.0ml/min.) to obtain 5 peptides. The peptides were analysed to determined their amino acid sequences ((1)-(5) mixed and kneaded with carrier vehicles, and compressed to prepare granules.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B04-C01B; B14-F02B1; D05-H13